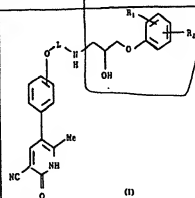


91-08869/13 803 GLAX 22.07.87
GLAXO INC. 09.03.90:45-565297 [+US-411065] (27.03.91) A61k-31/43
C06S31/35
New phenoxy-substit. pyridone nitrile(s) are used in treating
cardiovascular disease, esp. congestive heart failure
C11-457751 RJAT BE CH DE DK ES FR GB GR IT LI LU NL SE

Pyridone derivs. of formula (I) and their acid addn. salts
are new:

B(7-DAC, 12-FIC)



$R_1, R_2 = H, \text{ lower alkoxy, morpholino, CN, halo, CF}_3$
EP-419286-A*

alkyl (opt. substd. by alkoxy or cycloalkylalkoxy),
allylalkenyl, NO_2 , OH, alkenylalkoxy, NH_2 or mono-
or di-alkylamino;
 $L = (\text{CH}_2)_{p-1}, \text{CON}(\text{R}_1)\text{CR}_2\text{R}_3\text{R}_4$ (sp. (a)) or
 $(\text{CH}_2)_p$;
 $R_1 - R_4 =$ independently H or lower alkyl;
 $n = 1-3$;
 $p = 2-4$.

MORE SPECIFICALLY

$L = (a; n = 1-3)$ or $(b; p = 3)$ and OL is at the 4-position,
 R_1, R_2, R_3 and $R_4 = H$;
 R_5 and $R_6 = H$ or Me;
either

- (1) $R_1 = H$;
 $R_2 = \text{CN, Cl or Me}$;
- (2) $R_1 = H$;
 $R_2 = H, \text{CN or Cl}$; or
- (3) $R_1 = H$ or Cl;
 $R_2 = H, \text{CN or Cl}$ at the 2-position.

USE

(I) are positive inotropic and β -adrenergic agents useful
for treating congestive heart failure. Dose is 0.1-5 mg/kg 3-4
times a day.

SPECIFICALLY CLAIMED

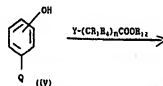
13 Cpts. (I) e.g. 5-(4-(N-(2-(3-phenoxy-1-hydroxy-
propylamino)ethyl)carbamoylmethoxy)phenyl)-6-methyl-2-
oxo-1,2-dihydro-3-pyridinecarbonitrile (1a);
5-(4-(N-(2-(3-(3-cyanophenoxy)-2-hydroxypropylamino)-
2-methylpropyl)carbamoylpropoxy)phenyl)-6-methyl-2-oxo-
1,2-dihydro-3-pyridinecarbonitrile; and
5-(4-(N-(2-(3-(2-chlorophenoxy)-2-hydroxypropylamino)-
2-methylpropyl)carbamoylmethoxy)phenyl)-6-methyl-2-oxo-
1,2-dihydro-3-pyridinecarbonitrile.

WIDER DISCLOSURE

Intermediates of formula (VI), (VII), (X), (XVI) and
(XVIII) are stated to form part of the invention.

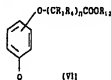
PREPARATION

(I)

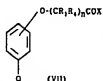


EP-419286-A*/1

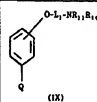
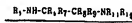
91-08869/13



(VI)



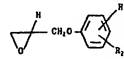
(VII)



(IX)



(X)



(XI)

(I; L=a)

EP-419286-A*/5

BEST AVAILABLE COPY

(cont)

(C) 2004 Copyright Derwent Information Ltd.

Q =



X = leaving gp. (e.g. OH);

Y = leaving gp.;

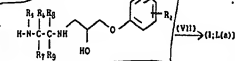
R₁₁ = H;

R₁₁ = amino protecting gp.;

or R₁₁ + R₁₂ = amino protecting gp.;

L₁ = (a)

(II)



(III)

(IV) Y-(CR₁₀R₁₁)_pNR₁₂R₁₃



L₁ = (b)

EXAMPLE

A soln. of 500 mg 5-(4-carboxymethoxyphenyl)-6-methyl-2-oxo-1,2-dihydro-3-pyridinecarboximide, 407 mg (5)-

EP-419285-A/3

91-08889/13

-N-(2-aminoethyl)-3-hydroxy-3-phenoxypyrrolidine and 316 mg diethyl cyanophosphonate in 10 ml DMF is cooled (ice bath) and treated dropwise with 540 µl Et₃N in 2 ml DMF. The mixt. is allowed to slowly warm to room temp., stirred overnight under N₂ then swged. in vacuo. The residue is chromatographed over silica gel, eluting with CHCl₃/MeOH/NH₄OH (50:10:1). The solid is recrystd. from EtOAc/MeOH to give 185 mg (21k) (1a), m.pt. 135-138°C. (29pp815HBDwgMo/d)

(E) 1SR: No Search Report.

EP-419285-A/4

BEST AVAILABLE COPY